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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Abuse and addictive potential of pregabalin

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SUMMARY
Introduction In the Republic of Serbia, pregabalin was marketed for the first time in 2006. Although the abuse of pregabalin has not been a common topic in the literature so far, it is often seen in everyday practice. Also, it seems that it is more common among addicts.
Case outline We report on a 41-year-old male patient who has a long history of multiple substance abuse and is currently undergoing buprenorphine substitution therapy. He began using pregabalin because it caused euphoria and elevated mood, in daily doses which varies between 1050–2100 mg. The highest daily dose was 4200 mg. At the time he was admitted to the hospital for pregabalin detoxification, he met the general criteria for addiction syndrome. On admission, the patient was tense, anxious, irritable, drenched in sweat, and had insomnia. With an adequate dose of buprenorphine, the patient continued to complain about the reduction of the pregabalin dose and insisted on adjusting the dose. Shortly, he was discharged from hospital at his personal request. After a month, during the check-up examination, he was diagnosed with a relapse of pregabalin use. He was readmitted to the hospital for detoxification treatment, the pregabalin dose was gradually reduced by 100 mg per week. After that the patient went to therapeutic community to continue treatment.
Conclusion This case indicates that practitioners have to be cautious when prescribing pregabalin to people prone to addiction. Further research is needed to identify risk factors for the development of pregabalin abuse syndrome, as well as to create clear guidelines for the treatment of abstinence syndrome.
Keywords: pregabalin; addiction; abuse; abstinence syndrome

INTRODUCTION

Pregabalin is an analog of gamma-amino butyric acid (GABA), and its effect is achieved by binding to an auxiliary subunit (62-д protein) of voltage-dependent calcium channels in the central nervous system [1]. There are several therapeutic indications for the use of pregabalin. In Serbia, it is used in the treatment of neuropathic pain, and epilepsy, as well as for treating generalized anxiety disorder [2]. Depending on the indication, the daily dose of pregabalin ranges from 150 to 600 mg. In the Republic of Serbia, it was first marketed in 2006. Although so far abuse and dependence on pregabalin have not been common topics in the available literature, it can be said that doctors often come across these cases in everyday practice. This has been noted both in Serbia and other countries [3, 4, 5]. Also, it seems that it is more common among addicts [6]. A study conducted in Serbia processed the results of toxicological and chemical analyses of blood and urine in postmortem cases in 2019, which recorded the potential risks of pregabalin abuse that can lead to addiction and severe poisoning with a fatal outcome [7]. For this reason, in some countries, a special warning has been added to the prescription of the drug, to increase caution when prescribing pregabalin to persons with a history of substance abuse [8]. The case report stresses out the importance of special caution when prescribing pregabalin.

This study was approved by the local ethics committee according to the Declaration of Helsinki.

CASE REPORT

We present a 41-year-old male patient who has been treated several times because of mental disorder due to psychoactive substances at the Clinic of Psychiatry, University Clinical Center of Vojvodina in Novi Sad. He is an unemployed construction technician, divorced, and has three children. Family history of mental disorders as well as his history of somatic illnesses is negative. As a patient with a long history of multiple substance abuse, he started abusing diazepam and tramadol during seventh grade of elementary school. When he was in high school his parents divorced, and he started consuming other substances such as tetrahydrocannabinol (THC), cocaine, stimulants, and finally heroin, which he used intranasally. At the age of 28, he went to the therapeutic community for detoxification treatment, where he stayed for a year. After leaving the therapeutic community, and after a short period of abstinence, he started using psychoactive substances again. In 2017, he consumed mostly opiates (buprenorphine 16–24 mg per day), which he procured illegally. In September 2018, he went to an outpatient psychiatrist when, in addition to the diagnosis of opiate addiction, he was

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diagnosed with generalized anxiety disorder and a mild depressive episode. Diagnoses were established according to the criteria of the International Classification of Diseases 10 Version (ICD-10) (F11.2, F41.1, F32.0) and antidepressants and pregabalin were introduced into the therapy [9]. In November of the same year, he was hospitalized for the first time at the Psychiatric Clinic to receive buprenorphine substitution therapy. The hospital discharge list included: Buprenorphine 10 mg, escitalopram 20 mg, pregabalin 150 mg, mirtazapine 15 mg. After leaving the hospital, he was non-compliant when it came to therapy and check-in examinations. The fact that he was unstable in the buprenorphine program, he was admitted to the hospital for the second time in December 2019. During the second hospitalization, buprenorphine therapy was reintroduced. This time, the hospital discharge list included: buprenorphine 16 mg, escitalopram 20 mg, and mirtazapine 15 mg. Shortly after leaving the hospital, following the recommendation of a friend, he started abusing pregabalin in the initial dose of 1575 mg. Side-effects after the initial dose manifested in the form of imbalance, dizziness, headache, and inarticulate movements. Because of this, he reduced the dose of pregabalin to 1050 mg, and sporadically took the stated dose with buprenorphine therapy on his own. The mentioned side effects did not occur during the next use. Pregabalin initially caused euphoria and elevated mood, and he described that the effects are similar to amphetamine (e.g., increased wakefulness, increased muscle strength). With pregabalin, he got the impression of an improved effect of buprenorphine therapy. Also, after the euphoria, it was easier for the patient to fall asleep and sleep peacefully for several hours. Occasional use of pregabalin gradually intensified and became more frequent, until the moment when the patient started using pregabalin every day for one year. Pregabalin was consumed orally, in the morning and the evening. Depending on the financial resources, the daily doses ranged from 1050 mg to 2100 mg. The highest daily dose consumed by the patient was 4200 mg divided into two doses (one in the morning and one in the evening). After a year, he came to see a psychiatrist wishing to start a pregabalin detoxification therapy. By that time, the patient had largely lost control of his pregabalin intake. On several occasions, he tried unsuccessfully to reduce the dose and stop using pregabalin. At that time the patient already met the general criteria for addiction syndrome according to the ICD-10 and showcased a strong desire to take the substance, had low self-control, demonstrated evidence of tolerance and physiological abstinence syndrome, and continued using the substance despite clear facts about undeniable harmful consequences [9]. Due to the impossibility of establishing abstinence in external conditions, the patient was hospitalized at the Psychiatric Clinic for the third time. Before the hospitalization, the patient took pregabalin at a daily dose of 2100 mg. Buprenorphine was taken for the last time a day prior to admission. Upon admission, the patient was tense, anxious, irritable, suffering from insomnia, and excessive sweating. According to the prescription, the maximum recommended daily dose of pregabalin is 600 mg, as well as valproate (750 mg), anxiolytic (diazepam 40 mg), and hypnotic therapy (midazolam 15 mg) to alleviate the symptoms of withdrawal syndrome. The laboratory analysis of sampled blood showed that there were no significant deviations from the reference values. Discontinuation of pregabalin therapy has been initiated. The patient was stable on the adequate dose of buprenorphine. However, the patient complained about the reduction of the pregabalin dose and still insisted on the pregabalin dose increase. In those moments, abstinence symptoms in the form of anxiety, irritability, tremor, and psychomotor restlessness were observed. There was a partial reduction of withdrawal symptoms during the 11 days of hospitalization with the contribution of the following therapy: diazepam 40 mg, pregabalin 300 mg, midazolam 15 mg, sertraline 100 mg, and valproate 1500 mg. On day 11 of hospitalization, the patient insisted on being discharged from the hospital. As there were no indications for hospitalization against his will, he was discharged. After a month, he appeared at the scheduled check-up. He was in good general condition, and stable on buprenorphine substitution therapy. However, he demonstrated low self-control and a strong craving for taking pregabalin and continued taking it despite the clear facts about the undeniable harmful consequences. One week before the control examination, he started abusing pregabalin again at a dose of 1200 mg per day. Excluding buprenorphine, the urine test tested negative for the presence of other psychoactive substances. The fourth hospitalization was initiated during which pregabalin (dose reduced by 100 mg per week) was discontinued. The patient was hospitalized for 45 days, during which the symptoms of abstinence syndrome were reduced, the day-night rhythm was established, and symptoms and signs of anxiety were reduced, with full insight and motivation for maintaining abstinence. The process of detoxification passed without major complications. The patient struggled with maintaining abstinence in the external environment which is why he continued his treatment in the therapeutic community, where, he spent the next four months. He is going to regular check-ups to this day.

DISCUSSION

In the case of our patient, the observed symptoms and signs of withdrawal syndrome are similar to those caused by the benzodiazepines (BZDs) and opiates. However, it is interesting to note that while being stable on buprenorphine substitution (i.e., using the drug in a prescribed manner), the patient did not feel the urge and abuse other substances, but still resorted to pregabalin. Even though pregabalin is most often used for the treatment of epilepsy and neuropathic pain, it is increasingly prescribed for the treatment of generalized anxiety disorder. One gets the impression that neither the doctors who prescribe this medicine nor the patients are fully aware of the risk of addiction that pregabalin carries. In Serbia and many other countries, there are no official guidelines for the treatment of pregabalin addiction and abstinence syndrome caused

by pregabalin cessation. The National Health Service in the United Kingdom has issued a detailed instruction, i.e., a scheme for reducing the dose of pregabalin when treating non-cancerous pain in primary health care [10]. Therefore, we were using BZDs and mood stabilizers in treating symptoms of the abstinence syndrome. As identified in other similar case reports, our patient also had medical history related to a behavioral disorder caused by substance use (THC, BZD, opiates) [8, 11, 12, 13]. According to the prescription, it is not recommended to combine BZD and pregabalin therapy. For this reason, we should bear in mind the importance of accurately informing patients about the potential risk of addiction when prescribing pregabalin, especially in the case of addicts. Although there are studies that indicate the risk of abuse and addiction, mental and behavioral disorders due to the use of pregabalin did not yet get the public attention they deserve [14, 15, 16]. Regarding the mechanism of pregabalin abuse at the biological level, research results are still heterogeneous and inconsistent but in the majority of cases they are in favor of pregabalin modulatory effects on the GABA and glutamate systems. One of the studies conducted on mice, investigating potential glutamatergic mechanisms, explored the involvement of glutamate in pregabalin-seeking behavior by using ceftriaxone, a potent glutamate transporter-1 up regulator. Mice that received doses of 60 and 90 mg/kg of pregabalin demonstrated drug-seeking-like behavior, which was effectively suppressed when they were pretreated with ceftriaxone [17]. The findings indicate that ceftriaxone effectively modulated the pregabalin-induced conditioned place preference, highlighting its potential as a promising candidate for developing treatments aimed at addressing pregabalin abuse. In line with this, another study states that pregabalin has the ability to influence the GABA and glutamate systems, which suggests the possibility of its potential for misuse, as well as an explanation for the development of withdrawal syndrome [18]. As we mentioned before and due to the fact that pregabalin's effect is achieved by binding to an б2-д protein of voltage-gate calcium channels, studies have shown that pregabalin and similar substances effectively inhibit the release of synaptic transmitters, particularly glutamate and norepinephrine, which are responsible for excitatory signals. They also induce a moderate increase in extracellular GABA levels in the brain, in a dose-dependent manner, resulting in mild GABA-mimetic effects such as relaxation and euphoria. These effects are commonly experienced at the start of drug therapy and after the use of higher-than-recommended doses [15]. Also, the authors of another study aimed to investigate the potential role of dopamine receptor-1 in the development of pregabalin-induced conditioned place preference [19]. Mice were assigned randomly to receive either saline or the dopamine-1 receptor antagonist SKF-83566. Among the group treated with pregabalin, a significant increase in the duration spent in the chamber associated with the drug was observed compared to the time spent in the chamber associated with the vehicle. Importantly, the administration of SKF-83566, which blocks dopamine-1 receptors, completely abolished the place preference induced by pregabalin, indicating the involvement of the dopaminergic system in pregabalin-induced reward-related behavior.

This case report stresses the importance of special caution when prescribing pregabalin. It indicates precautionary measures to keep in mind when prescribing pregabalin to individuals prone to substance abuse or dependence. It is clear that these individuals stood out as a vulnerable group, but further research is needed to identify risk factors for the development of pregabalin abuse and dependence. As in our case, the most probable reason for the abuse of pregabalin lies in its euphoric effects. The effects of pregabalin when administered correctly are not questioned. Lastly, clear guidelines are needed for the treatment of abuse and abstinence syndrome in pregabalin addiction, which seems to have pandemic potential according to our experience.

Conflict of interest: None declared.

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Злоупотреба и потенцијал прегабалина да створи зависност

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САЖЕТАК

Увод На територији Републике Србије прегабалин је први пут стављен у промет 2006. године. Иако до сада злоупотреба прегабалина није била честа тема у литератури, лекари је често могу видети у свакодневној пракси. Такође, чини се да је она чешће заступљена међу особама које су зависници.

Приказ болесника Приказујемо 41-годишњег болесника мушког пола, који има дугу историју вишеструке злоупотребе супстанци и који је тренутно подвргнут супституционој терапији бупренорфином. Прегабалин почиње да злоупотребљава због ефекта еуфорије и повишеног расположења и то у просечној дневној дози 1050–2100 *mg*. Највиша дневна доза коју је конзумирао била је 4200 *mg*. У моменту када је примљен у болницу ради детоксикације испуњавао је опште критеријуме за синдром зависности. При пријему је био напет, узнемирен, раздражљив, анксиозан, обливен знојем, имао је несаницу. По ординирању адекватне дозе бупренорфина, жалио се због смањења дозе прегабалина, те је инсистирао на њеној корекцији. Отпуштен је на лични захтев. На контролном прегледу после месец дана дијагностикован је рецидив злоупотребе прегабалина. Поново је примљен у болницу ради детоксикационог третмана. Доза прегабалина је постепено смањивана, 100 *mg* недељно. После тога је болесник упућен у терапијску заједницу да би наставио лечење.

Закључак Овај случај указује на мере опреза које лекари треба да имају приликом прописивања прегабалина особама склоним развоју зависности. Потребна су даља истраживања ради идентификовања фактора ризика за развој злоупотребе прегабалина, као и јасне смернице за третман апстиненцијалног синдрома.

Кључне речи: прегабалин; зависност; злоупотреба; апстиненцијални синдром